Remarks

Claims 88-101 and 103-104 are pending. Claims 2-41 have been previously cancelled. Claims 1, 42-88, 102, and 105-131 have been withdrawn from further consideration as being drawn to non-elected inventions. No new matter has been added.

Rejections Under 35 U.S.C. §112

The Examiner maintained the rejection of claims 88-101, 103 and 104 under 35 U.S.C. §112 as lacking enablement.

It is Applicants belief that the Examiner has misunderstood Applicants arguments presented in the response to first Office Action and has not presented any reasonable scientific basis for rejecting Applicants' assertions. Each of these points is addressed below.

In response to Applicants remarks, the Examiner has stated that "Applicants argue that examples have been provided in the art that describe various examples of the in vivo administration of antisense oligonucleotides, and that these examples enable one skilled in the art to practice the instant invention over the scope claimed." The Examiner then addresses the teachings of Bayever et al, Cossum et al and Agrawal et al. Applicant presented these 3 references after several other arguments and solely for the purpose of demonstrating a "correlation between *in vitro* assays for antisense oligonucleotides to that of *in vivo* dosing parameters for oligonucleotides". (Applicants Response Dated September 30, 2002, Paper No. 12, Page 7) The purpose of the citation was to demonstrate that "the *in vitro* assays described in the specification can easily be translated into *in vivo* dosing parameters for oligonucleotides by those of ordinary skill in the art." (Applicants Response Dated September 30, 2002, Paper No. 12, Page 7) Prior to this statement, the following additional arguments were presented. The Examiner has not addressed any of these arguments.

1. The specification includes a thorough description of the invention that would enable one of skill in the art to select a CpG containing oligonucleotide and to administer it to a subject to treat an infectious disease. The specification also provides many working examples.

Claims 88-101 and 103-104 relate to methods for treating and preventing bacterial infection in a subject. The specification on page 9, lines 5-7 teaches that the CpG oligonucleotides of the invention are useful for treating and preventing bacterial infection. An extensive list of infectious bacteria is presented on pages 14-15. A detailed description of CpG immunostimulatory nucleic acids useful in treating immune deficiencies for the treatment and prevention of bacterial infection is presented on pages 15-17. Methods for determining the stimulation index of a particular CpG DNA as presented on pages 17-18 stabilize nucleic acids are described on page 18-19. Pages 20-42 describe actual working examples demonstrating B cell activation, NK activation, induction of cytokines, such as IL6, and IL12 using many different oligonucleotides containing CpG having different backbones, under different

conditions, using different dosages. Although working examples are not required in a patent application, many working examples have been provided.

The specification provides adequate guidance concerning route of administration, types of oligonucleotides and dosages. For example, Applicants have described the type of administration, e.g., see page 54, lines 6-20. Applicants have described times or frequencies of administration, for example, see page 53, lines 5-11 and 19-25. Effective amounts and manner of determining effective amounts to obtain the desired effects are described in the specification, for example, page 54, line 21-page 55, line 1.

2. A recent review article (copy attached to Applicants Response Dated September 30, 2002, Paper No. 12, as Exhibit 4) confirms that one of skill in the art can successfully treat infectious disease as set forth in detail in the specification.

One of skill in the art would have no reason to doubt a correlation between the data presented in the specification and the claimed invention of treating or preventing bacterial infections. Applicant has clearly demonstrated that a variety of CpG containing oligonucleotides can stimulate B cell activation, NK cell activation, and cytokine induction. The attached paper is a review article describing the effects of CpG in activating innate immune defenses against infections. (Krieg, A., *Annu. Rev. Immunol.*, 20:709 (2002)). The review article describes several studies in which CpG was used successfully to treat and prevent different types of infectious disease in vivo (p. 728-29). CpG functions by activating an immune response to attack and kill the invading bacteria. This general immune response should be effective against bacteria in general, rather than being limited to a specific type of bacteria.

The second reason provided by the Examiner for maintaining the rejection, is not based on any scientific facts. The Examiner has simply stated that the data presented cannot be extrapolated and is not representative of the full scope of the claims. Applicants have provided scientific evidence in the form of working examples as well as a review article describing in vivo studies resulting in the successful treatment of infectious disease. A statement that such data is insufficient to support the full scope of the claims and nothing else is not sufficient to support a prima facie case of lack of enablement. The Examiner has made two points in the response.

The first point is that working examples demonstrating B cell and NK cell activation is not sufficient to demonstrate that the claimed compounds are useful for treating bacterial infections. B cells and NK cells are immune cells that are involved in producing an immune response to infectious disease. It is unclear why the examiner believes that the data presented in the specification related to B cell and NK cell activation is not relevant to the claimed method of

treating bacterial infection. It is requested that such a rejection be supported by scientific evidence in the form of publications or even general knowledge in the art.

The second point is that "the inclusion of the CpG motif within an oligonucleotide is necessary but not sufficient for generating predictable immune responses in an organism". The Examiner has not presented any support for this statement, which is contrary to Applicants understanding of CpG oligonucleotides. Certain CpG containing oligonucleotides have higher activity than others based on the particular motifs, number of CpGs, length of the oligonucleotide etc. Many of these parameters are described in the specification in detail. Although some CpG containing oligonucleotides are less active than others, an oligonucleotide containing a CpG motif is useful for promoting an immune response. The specification describes ways for enhancing immune stimulation e.g., by using a nucleic acid delivery complex or other formulations. Applicants disagree with the Examiners conclusion that a "CpG motif within an oligonucleotide is necessary but not sufficient".

Finally, the Examiner has failed to address Applicants' point that CpG has been demonstrated to be useful in treating infectious disease *in vivo* (Krieg, A., *Annu. Rev. Immunol.*, 20:709 (2002)). This point must be addressed.

Accordingly, withdrawal of this rejection is respectfully requested.

Rejections Under Non-statutory Double Patenting

The Examiner rejected claims 88-101, 103, 104 under the non-statutory double patenting doctrine as being unpatentable over US Patent Nos. 6,207,646; 6,194,388; and 6,239,116. If the other rejections are withdrawn applicants will consider filing a terminal disclaimer to overcome the rejection.

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

A request for continued examination (RCE) and a request for extension of time is included with this filing, along with a check in the amount $1,680 for the RCE and three for extension of time. If any further fee is due with this response, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

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Docket No. C01039.70042.US
Date: August 18, 2003
x08/25/03